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10/525,624	11/03/2005	Jean-Luc Puel	DURE-034	9637

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EXAMINER	
RODRIGUEZ-GARCIA, VALERIE	
ART UNIT	PAPER NUMBER
1626	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,624	PUEL ET AL.	
	Examiner	Art Unit	
	VALERIE RODRIGUEZ-GARCIA	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11-10-2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

VRG

DETAILED ACTION

Status of the Claims

Claims 1-19 are currently pending.

1. Applicant's election with traverse of Group III, claims 14-18 and newly added claim 19, in the reply filed on 11/10/2008 is acknowledged. The following elected species is also acknowledged: gacyclidine.

The traversal is on the ground(s) that the special technical feature that fulfills the PCT requirements comprises a drug or agent that modulates glutamate-mediated neurotransmission or sodium channel function without causing significant clinical hearing loss associated with suppression of AMPA receptor-mediated signals. Applicants further comment that the NMDA antagonists listed in US Patent 5,039,528 (cited in the restriction requirement) are not useful in the practice of the claimed invention. Applicant's invention recites D-AP5 and 7-chlorokynurenate as drugs that fulfill the invention requirements (see instant claims 6, 9 and 16). However, D-AP5 and 7-chlorokynurenate are also disclosed in US Patent 5,039,528.

Applicant's arguments are not found persuasive because under PCT rule 13.1 a group of inventions should be so linked as to form a single general inventive concept. However, there is lack of inventive concept, due that the composition and methods claimed by applicants have been previously disclosed in US Patent 5,039,528 (cited in the restriction requirement and international search report). As such, they lack a special technical feature. The reasoning above also applies to the species election.

Therefore, the requirement is still **maintained**.

Claims 1-13 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/10/2008.

Priority

This application is a 371 of PCT/US02/28519 filed on 09/06/2002.

Information Disclosure Statement

No Information Disclosure Statements have been filed in the present application. Applicants are reminded of their duty to disclose patents and publication relevant to the patentability of the instant claims.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Note

Pursuant to Applicant's response, claims 1-19 are pending, claims 1-13 are withdrawn and claims 14-19 are treated on the merits in this action. This is the first Office Action on the merits of the claims.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The term "agent that modulates glutamate-mediated neurotransmission or sodium channel function", recited in claim 14, has not been properly disclosed in the application. The disclosure and claims 14 and 15 describe an "agent" by its biological property or function rather than by its structure. Applicants have not specified the "agent" of which patent protection is being sought. As such, the skilled artisan would not recognize, know how to make and use the invention. Moreover, the Specification provides only for the use of some NMDA receptor antagonists. The Specification does not describe any other compounds so as to convey possession of the entire genus encompassed by the general term "agent" that modulates glutamate-mediated neurotransmission or sodium channel function of claim 14. As such, the instant claims 14-19 lack support in the specification.

3. Claims 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The specification and claims have not properly described which ones of the formulations, NMDA receptor antagonists and "derivatives or analogues thereof", as recited, don't cause hearing loss (claims 14-16). As such, the skilled artisan would not recognize, know how to make and use the invention. Which "derivatives or analogues thereof" have those properties? As such, the instant claims 14-19 lack support in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 14-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation "significant clinical hearing loss" of claim 14 is a relative term which renders the claims indefinite. The term "significant" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear what is encompassed and excluded

by the limitation "significant clinical hearing loss". The meaning of "significant" is defined by the Merriam-Webster's Dictionary as "especially, having meaning or having influence or effect". Thus, how much hearing loss is "significant hearing loss"? One of ordinary skill could not ascertain and interpret the metes and bounds of the patent protection desired as to these terms.

5. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of "derivatives or analogues thereof" renders the claim indefinite. The term "derivatives or analogues thereof" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear what is encompassed and excluded by the limitation "derivatives or analogues thereof". The Merriam-Webster's Dictionary defines "derivative" as "a chemical substance related structurally to another substance and theoretically derivable from it". Hence, one of ordinary skill would clearly recognize that derivatives or analogues of the drugs claimed in claim 16, would read on any of those compounds having any widely varying groups that possibly substitute the compounds. One of ordinary skill could not ascertain and interpret the metes and bounds of the patent protection desired as to these terms. Thus, it is unclear and indefinite as to how "derivatives or analogues thereof" herein are encompassed thereby.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 14-16 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Liu *et al.* (Toxicol. Appl. Pharmacol., **1995**; 132: 196-202).

Liu *et al.* teaches the protective effect of MK-801 against carbon monoxide-induced hearing loss (title). Liu *et al.* disclose that cochlear impairment induced by CO hypoxia may result from excess extracellular concentrations of glutamate (last line of abstract). CO administration impairs auditory function by inducing an abnormal release of endogenous glutamate (p.199, 2nd col.). MK-801 applied topically to the round window and allowed to permeate through the round window membrane directly into the cochlea of guinea pigs (p. 197, 2nd col., 3rd paragraph) resulted in long term protection of cochlear function (p.198, 2nd col., 28-30).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu *et al.* (Toxicol. Appl. Pharmacol., **1995**; 132: 196-202) in view of US 5,039,528, further in view of US 6,265,379 B1.

Liu *et al.* teach the protective effect of the NMDA antagonist MK-801 against carbon monoxide-induced hearing loss (title). Liu *et al.* disclose that cochlear impairment induced by CO hypoxia may result from excess extracellular concentrations of glutamate (last line of abstract). CO administration impairs auditory function by inducing an abnormal release of endogenous glutamate (p.199, 2nd col.). MK-801 applied topically to the round window and allowed to permeate through the round window membrane directly into the cochlea of guinea pigs (p. 197, 2nd col., 3rd paragraph) resulted in long term protection of cochlear function (p.198, 2nd col., 28-30).

What it lacks is the administration of at least about 3 days, the delivery rate of about 0.1 mg per hour to 200 mg per hour continually and wherein the disorder comprises tinnitus.

However, US 5,039,528 teaches the administration of NMDA antagonist D-AP5 to dogs, intravenously, at doses of 5 mg/kg. If a young adult dog weights about 7 kg, a

dose administered to the dog could be 5 mg/kg x 7 kg = 35 mg. US 5,039,528 further teaches that one or more tests would be done using NMDA to determine an effective dosage for an individual dog (col. 15, lines 44-59). The cited reference is evidence that it is part of routine medical experimentation/diagnosis to determine optimum effective dosages and periods of time of drug administration necessary for the treatment of individual patients.

As such, it would have been prima facie obvious to a person of ordinary skill at the time of the invention to administer the NMDA antagonist MK-801 to the inner ear through the round window membrane for its protective effects to the cochlea, as taught by Liu *et al.*, for a period lasting until full protection has been achieved. Furthermore, it would have been prima facie obvious to deliver the drug for a period of 3 days, at a rate of about 0.1 mg per hour to 200 mg per hour in expectation of successfully determining the optimum effective dosages and the optimum period of drug administration necessary for the claimed treatment, as evidenced by US 5,039,528.

In regards to the disorder comprising tinnitus, US 6,265,379 B1 teaches that tinnitus; particularly inner ear tinnitus is due to cochlear nerve dysfunction (column 2, lines 54-55). US 6,265,379 B1 teaches local administration for the treatment of tinnitus includes injection (column 5, lines 62-67).

It would have been obvious to one of ordinary skill in the art to use NMDA antagonist MK-801 for the treatment of tinnitus caused by cochlear impairment induced by carbon monoxide, because Liu *et al.* teach the protective effects of MK-801 applied topically to the cochlea (p. 201, 3rd paragraph) and because tinnitus is a disorder of

cochlea as taught by US 6,265,379 B1. One would have been motivated to employ a formulation comprising MK-801 for the treatment of tinnitus in a subject suffering from tinnitus, in order to achieve an expected benefit of protection of cochlea as shown by *in vivo* experimentation by Liu *et al.*.

8. Claims 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu *et al.* (Toxicol. Appl. Pharmacol., **1995**; 132: 196-202) in view of Laplanche *et al.* (Neuroscience Lett. 2000; 289: 49-52).

The teachings of Liu *et al.* has been disclosed above.

What it lacks is the NMDA receptor antagonist gacyclidine.

Laplanche *et al.* disclose that the NMDA antagonist gacyclidine blocks the hydroxyl radicals release induced by massive and presumably toxic infusion of glutamate (p. 51, 1st col., lines 6-9). It further compares gacyclidine with MK-801, reciting that MK-801 has an unexpected toxicity when used in vivo (p. 49, 1st column, last paragraph) and it is less efficient than gacyclidine (p. 51, 1st col., lines 25-32).

As such, it would have been prima facie obvious to a person of ordinary skill at the time of the invention to administer gacyclidine, because of less toxicity and stronger protective effects against glutamate excitotoxicity, as disclosed by Laplanche *et al.*, in the method of Liu *et al.* of administering an NMPA receptor antagonist to the inner ear through the round window membrane.

9. Claims 14-15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2004/0102525 A1.

US 2004/0102525 A1 discloses the use of the NMDA antagonist memantine for the treatment of tinnitus caused by a cochlear lesion induced by excessive glutamate release (p. 25, [0192, 0193, 0194 and 0195]). Memantine is administered orally in doses of 5-100 mg/day.

What it lacks is the administration through the round window membrane of the subject.

However, administration of the drug by passing it through the round window membrane and into the inner ear of the subject is obvious because the affected area is the inner ear, therefore, one of ordinary skill in the art would direct the administration of the drug in or to the vicinity of the inner ear in order to optimize the protection of cochlear damage.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 14-15 and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 5 of copending Application No. 10/812298 in view of Liu *et al.* (Toxicol. Appl. Pharmacol., **1995**; 132: 196-202). The instant claims recite a method of treating an inner ear disorder, the disorder comprising tinnitus, caused by aberrant glutamate-mediated neurotransmission, by administering to a round window membrane of a subject a NMDA receptor antagonist. Liu *et al.* disclose that cochlear excitotoxicity results from excess concentrations of glutamate (abstract and p. 198, 2nd col., last lines). As such, it is obvious that the tinnitus induced by cochlear excitotoxicity of application 10/812298 is the same as the ear disorder caused by aberrant glutamate-mediated neurotransmission of the instant application. The difference in the claims is also that claims 1 and 5 of copending Application No. 10/812298 are broader.

This is a provisional obviousness-type double patenting rejection.

11. Claims 14-16 and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 5 of

copending Application No. 11/236941 in view of Liu *et al.* (Toxicol. Appl. Pharmacol., **1995**; 132: 196-202). The instant claims recite a method of treating an inner ear disorder, the disorder comprising tinnitus, caused by aberrant glutamate-mediated neurotransmission, by administering to a round window membrane of a subject a NMDA receptor antagonist. Liu *et al.* disclose that cochlear excitotoxicity results from excess concentrations of glutamate (abstract and p. 198, 2nd col., last lines). As such, it is obvious that the tinnitus induced by cochlear excitotoxicity of application 11/236941 is the same as the ear disorder caused by aberrant glutamate-mediated neurotransmission of the instant application. The difference in the claims is also that claims 1-6 and 17 of copending Application No. 11/236941 are broader.
This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to VALERIE RODRIGUEZ-GARCIA whose telephone number is (571)270-5865. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Kamal A Saeed/
Primary Examiner, Art Unit 1626